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Enantiomers of phenoxy derivatives of
benzyl morpholine and salts thereof

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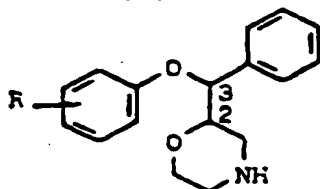
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Ther. Vol 19, No 3, 1984,
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C2C

**"ENANTIOMERS OF PHENOXY DERIVATIVES OF BENZYL
MORPHOLINE AND SALTS THEREOF"**

The present invention relates to RR and SS enantiomers of phenoxy derivatives of benzyl morpholine and salts thereof, to a process for their preparation and to pharmaceutical compositions containing them.

- 5 U.S. patent No. 4,229,449 describes, among the others, 2-(*d*-phenoxy-benzyl)-morpholine derivatives of the following formula (I)



(I)

- 10 wherein R is a C₁-C₆ alkoxy group or a trihalomethyl group, and their pharmaceutically acceptable salts. Due to the presence of the two chiral centers at the carbon atoms 2 and 3 in the above formula (I), for each compound of formula (I) two couples of enantiomers exist. These two couples, which are in a diastereoisomeric relationship one to the other, are identified by
- 15 the symbols (-) RS, RS and, respectively (+) RS, SR, in accordance with IUPAC, NOMENCLATURE OF ORGANIC CHEMISTRY, 1979 Edition, Section E, 489.

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In the formula (I) and in the other formulae of this specification the two chiral centers have been conventionally numbered 2 and 3 in order to be able to indicate unequivocally the absolute configuration of each center, when available. Such a conventional numbering, however, is independent of the numbering required, e.g. by the IUPAC Nomenclature, for a correct naming of the involved compounds.

While mention of specific diastereoisomers, i.e. couples of enantiomers, of the above formula (I) was given in U.S. Patent No. 4, 229,449, no specific mention was therein made of the single enantiomers deriving therefrom.

The present invention provides a 2R, 3R or 2S, 3S enantiomer of a compound of formula (I) and the pharmaceutically acceptable salts thereof. An enantiomer of the invention will therefore be either a dextro (+) or a levo (-) enantiomer. Preferred compounds of the invention are those wherein R is methoxy, ethoxy or trifluoromethyl.

The present invention includes also the bioprecursors and, as already said, the pharmaceutically acceptable salts of the 2R, 3R or 2S, 3S enantiomers

formula (I), as well as the pharmaceutical compositions containing the said enantiomers or their salts.

Examples of pharmaceutically acceptable salts of the enantiomers of the invention are both the

5 salts with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulphuric acid, and the salts with organic acids, including optically active acids, for example, citric acid, tartaric acid, methanesulphonic acid, fumaric acid, maleic acid and mandelic acid.

10 Preferred salts are those with hydrochloric acid and methanesulphonic acid, the more preferred ones being those with methanesulphonic acid.

Examples of specific preferred compounds of the invention are the following (+) and (-) enantiomers:

- 15 (+)-2-[4-(2-methoxy-phenoxy)-benzyl]-morpholine;
(-)-2-[4-(2-methoxy-phenoxy)-benzyl]-morpholine;
(+)-2-[4-(2-ethoxy-phenoxy)-benzyl]-morpholine;
(-)-2-[4-(2-ethoxy-phenoxy)-benzyl]-morpholine;
(+)-2-[4-(4-trifluoromethyl-phenoxy)-benzyl]-morpholine;
20 (-)-2-[4-(4-trifluoromethyl-phenoxy)-benzyl]-morpholine,
and their pharmaceutically acceptable salts, in particular the salts with hydrochloric acid or methanesulphonic acid.
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The compounds of the invention may be prepared by a process comprising:

- 5 (a) reacting the (\pm)RS,RS racemic form of a compound of formula (I), as free base, with an optically active acid, so obtaining a mixture of two diastereoisomeric salts;
- (b) separating the obtained salts by crystallization;
- (c) optionally liberating the dextro (-) or levo (-) enantiomeric base from the respective separated
10 salt; and
- (d) optionally salifying the obtained dextro (-) or levo (-) enantiomeric base with a pharmaceutically acceptable acid.

15 The reaction of the (\pm)RS,RS racemic form of a compound of formula (I) as free base with an optically active acid may be carried out with any suitable optically active acid which may be, for instance, L (-) mandelic acid, D (-) mandelic acid, 10 (+) camphersulfonic acid, L (-) dibenzoyltartaric acid, L (-) pyrrolidon-carboxylic
20 acid, L (-) tartaric acid or D (-) tartaric acid.

This salification reaction is preferably performed in an organic, preferably anhydrous, solvent, which may be, for instance, methanol, ethanol, dioxane or dimethylformamide.

If necessary, the precipitation of the obtained salt from the reaction solvent may be favoured by adding an anhydrous apolar solvent which may be, for example, diethylether, n-hexane or cyclohexane.

5 The separation of the desired salt from the diastereoisomeric mixture is preferably carried out by fractional crystallization from an appropriate solvent which may be, for example, methanol or ethanol. Preferably an anhydrous solvent is used.

10 The optional liberation of the corresponding dextro (+) or levo (-) enantiomeric base from the separated salt may be carried out by treatment with a small excess of any suitable base. An inorganic base such as, for instance, an alkali metal or alkaline-earth metal
15 hydroxide or carbonate or bicarbonate, is preferably used. Sodium or potassium carbonate or bicarbonate are particularly preferred bases.

The optional salification of an obtained dextro (+) or levo (-) enantiomeric base may be carried out by
20 reaction with a stoichiometric amount or a small excess of the desired acid in an appropriate solvent. Thus, for example, the salt with hydrochloric acid may be obtained by treatment with anhydrous gaseous hydrochloric acid or an anhydrous alcoholic solution of
25 hydrochloric acid in an anhydrous solvent such as, e.g.,

diethylether, toluene, ethanol, and isolating the hydrochloride by filtration or evaporation of the solvent. Analogously, the salt with methanesulphonic acid may be obtained, for example, by adding an ethanolic solution of methanesulphonic acid to the ethanolic mixture of the enantiomeric base.

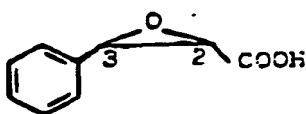
The precipitation of the methanesulphonate salt may be, if necessary, favoured by the addition of an anhydrous apolar solvent which may be for example, diethylether, n-hexane or cyclohexane.

All the reaction steps reported above from a) to d) may be carried out at a temperature varying from about 0°C to about 50°C, the room temperature being, in any case, the preferred one.

The preparation of the compounds of formula (I) as a mixture of diastereoisomers and as separated diastereoisomers is reported in U.S. patent No. 4,229,449. In an alternative approach, the

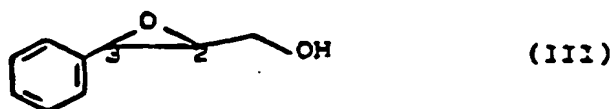
compounds of the invention may be prepared by a process comprising:

(a) reducing the (+) or (-) enantiomer of a glycidic acid of formula (II)



(II)

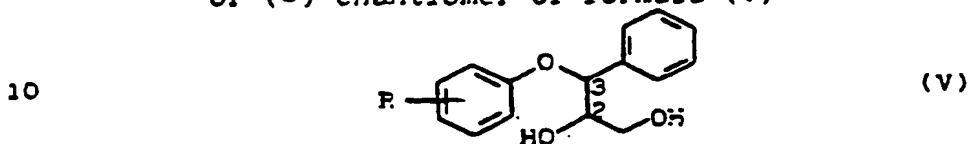
or a derivative thereof, so obtaining the (+) or (-) enantiomer of the cinnamyl alcohol-2,3-epoxide of formula (III)



- 5 (b) reacting a (+) or (-) enantiomer of formula (III) with a phenol derivative of formula (IV)

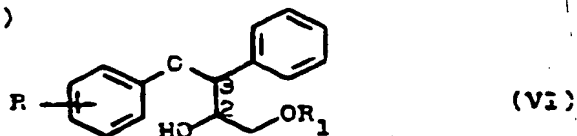


wherein R is as defined above, so obtaining a (+) or (-) enantiomer of formula (V)



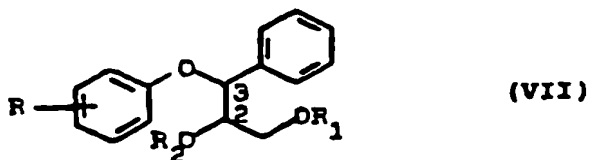
wherein R is as defined above;

- 10 (c) esterifying a (+) or (-) enantiomer of formula (V) with a carboxylic acid, or a reactive derivative thereof, so obtaining a (+) or (-) enantiomer of formula (VI)



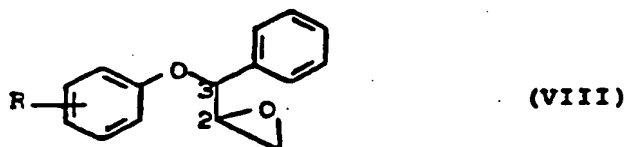
wherein R is as defined above and R₁ is the residue of a carboxylic acid;

- 20 (d) esterifying a (+) or (-) enantiomer of formula (VI) with a sulphonic acid, or a reactive derivative thereof, so obtaining a (+) or (-) enantiomer of formula (VII)



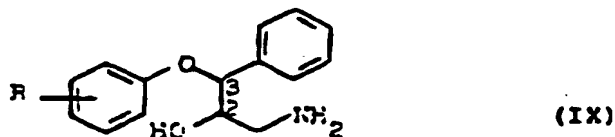
wherein R and R₁ are as defined above and R₂ is the residue of a sulphonic acid;

- (e) making an epoxide from a (+) or (-) enantiomer of formula (VII) in the presence of a base so obtaining a (+) or (-) enantiomer of formula (VIII)



wherein R is as defined above;

- (f) reacting a (+) or (-) enantiomer of formula (VIII) with ammonia, so obtaining a (+) or (-) enantiomer of formula (IX)

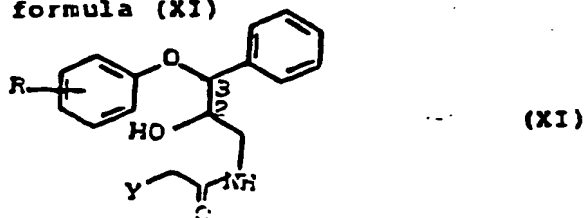


wherein R is as defined above;

- (g) reacting a (+) or (-) enantiomer of formula (IX) with compound of formula (X)

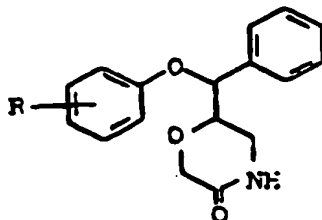


wherein Y is halogen, so obtaining a (+) or (-) enantiomer of formula (XI)



wherein R and Y are as defined above;

- (h) cyclizing a (+) or (-) enantiomer of formula (XI) so obtaining a (+) or (-) enantiomer of formula (XII)



(XII)

wherein R is as defined above; and

- (i) reducing a (+) or (-) enantiomer of formula (XII) so obtaining a (+) or (-) enantiomer of formula (I) and, if desired, converting the obtained 2R,3R or 2S,3S enantiomer of formula (I) into a pharmaceutically acceptable salt thereof.

A derivative of the glycidic acid of formula (II) may be, e.g., an anhydride, preferably a mixed anhydride. The carboxylic acid employed in the above esterification step (c) may be either aliphatic, e.g. a C₂-C₆ aliphatic carboxylic acid such as, for instance, acetic or propionic acid, or aromatic, e.g. benzoic or p-nitro-benzoic acid.

The R₁ residue of a carboxylic acid in the above formulae (VI) and (VII) is, e.g., acetyl, propionyl, benzoyl or p-nitro-benzoyl.

The sulphonic acid employed in the esterification step

(d) is, for example, methanesulphonic acid, thanesulphonic acid, benzenesulphonic acid or p-toluenesulphonic acid. The R_2 residue of a sulphonic acid in the above formula (VII) is, e.g., methanesulphonyl, ethanesulphonyl,

5 benzenesulphonyl or p-toluenesulphonyl, preferably methanesulphonyl. The halogen Y in the compounds of formula (X) and formula (XI) is, preferably, chlorine, bromine or iodine, most preferably chlorine.

The reduction step (a) may be carried out with BH_3 or
10 a mixed hydride such as, e.g., $NaBH_4$ following known procedures, preferably operating under cooling, e.g. around $0^\circ C$, in a suitable anhydrous inert solvent which may be, for instance, absolute ethanol, diethyl ether or tetrahydrofuran.

15 The reaction of an enantiomer of formula (III) with a compound of formula (IV) is preferably carried out by heating, e.g. at a temperature between about $60^\circ C$ and about $120^\circ C$, in the presence of a base such as, e.g., aqueous sodium or potassium hydroxide, preferably in
20 absence of any other solvent.

The esterification of an enantiomer of formula (V) to give a compound of formula (VI) is preferably performed with a reactive derivative of a carboxylic acid, preferably a carboxylic acid halide, in particular
25 chloride, operating under cooling, e.g. at about $-10^\circ C$ to $0^\circ C$, or at room temperature, in an anhydrous organic

solvent, e.g. benzene or toluene, in the presence of a base which may be, for example, an organic base such as, e.g., triethylamine or pyridine: according to a preferred procedure, pyridine is used as solvent in
5 absence of any other base.

The esterification of an enantiomer of formula (VI) to give a compound of formula (VII) is preferably carried out with a reactive derivative of a sulfonic acid, preferably a sulfonic acid halide, in particular the
10 chloride, e.g. methanesulfonyl chloride or p-toluenesulfonyl chloride, in the presence of an acid acceptor which may be, for instance, an organic base as triethylamine or pyridine.

The reaction is preferably performed under cooling, e.g. at -10°C to 5°C, in a suitable anhydrous solvent
15 such as, e.g., benzene, toluene, methylene chloride or pyridine: when pyridine is used as solvent, it also acts as a base.

The transformation of a compound of formula (VII) into a compound of formula (VIII), is carried out by reaction
20 with a suitable base, preferably an inorganic base such as, e.g., an alkali metal or alkaline-earth metal hydroxide, preferably sodium or potassium hydroxide. Preferably the reaction is carried out at room temperature in an aqueous organic solvent such as, e.g.
25 dioxane or dimethylformamide.

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The subsequent reaction of the epoxide of formula (VIII) with ammonia is preferably carried out at room temperature with 30-32% aqueous ammonia in a suitable solvent which may be, for instance, dimethylacetamide or an

5 aliphatic alcohol, e.g. methanol or ethanol.

The reaction between an obtained enantiomer of formula (IX) and a compound of formula (X) may be, e.g., performed in the presence of a base, e.g. an organic base such as, for instance, triethylamine, preferably operating

10 under cooling, for example at -10°C to 0°C , in an anhydrous inert solvent, e.g. an halogenated hydrocarbon such as, e.g., methylene chloride.

The subsequent cyclization of an enantiomer of formula (XI) may be, e.g., performed by treatment with a base, for example with potassium tert.butoxide in tert.butyl

15 alcohol at room temperature, according to known procedures.

The reduction of an obtained enantiomer of formula (XII) may be, e.g., carried out by treatment with BH_3 or a mixed hydride, for instance LiAlH_4 or NaBH_4 , in an

20 anhydrous inert solvent such as, e.g., diethylether, tetrahydrofuran, dioxane or toluene, at temperatures varying from about 0°C . to the reflux temperature; a particularly suitable reduction procedure involves the

25 use of Red-Al (Vitrider) as the reducing agent in

anhydrous toluene at room temperature .

The optional salification of an obtained enantiomer of formula (I) may be carried out in any conventional way according to known salification procedures.

5 The glycidic acid enantiomers of formula (II), used as starting material in the alternative process approach described above, are either known compounds or compounds that can be prepared by known methods from known compounds: see, for instance, K. Harada, J. Org. Chem.,
10 31, 1497, 1966.

The compounds of the invention are active on the central nervous system, in particular as antidepressant agents, as is shown, e.g., by their ability in raising the concentration of physiologically
15 active monoamines, e.g. by blocking their uptake and or by desensitizing α -2 presynaptic receptors.

As is known, an important property of antidepressant agents is their ability of blocking neurotransmitter uptake at cerebral synapses (Iversen L.L., J. Pharm.
20 Pharmacol., 17:42, 1965), and further important property may also be the ability of blocking or desensitizing α -2 adrenoceptors (Chapleo C.B., J. Med. Chem. 26:823, 1983).

25 The compounds of the invention were found to be able to increase the concentration of biogenic amines both.

in vitro (when activity was determined, e.g., with radioactively labelled compounds according to the experimental method described by Snyder S.H. in J. Pharmacol. Exp. Ther., 165:76, 1969) and in vivo by a variety of methods.

The physiologically active monoamines whose concentration is raised by the compounds of this invention include serotonin, norepinephrine and dopamine.

The antidepressant activity of the compounds of this invention is proved also by the fact that they are active in preventing reserpine-induced blepharospasm and hypothermia in mice.

The compounds of this invention may also find use, e.g., in treating disorders of sleep and as minor tranquilizers.

The toxicity of the compounds of the invention is negligible, therefore they can be safely used in therapy.

The compounds of the present invention are preferably administered orally, although they can be administered also in other conventional ways, for example, by injection or by rectal way.

The dosage suitable for the oral administration to adult humans of the compounds of the invention, is preferably 0.5-10 mg per dose 2-4 times a day.

Pharmaceutical compositions according to the invention comprise a 2R,3R or 2S,3S enantiomer of a compound of formula (I) or a pharmaceutically acceptable salt thereof as active ingredient and a pharmaceutically acceptable carrier and/or diluent. The

compositions may be prepared according to conventional methods with the usual ingredients. Thus, for oral administration, the pharmaceutical compositions containing the compounds of the invention
5 are preferably tablets, pills or capsules which contain the active substance together with diluents, such as, for example, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose; lubricants, for instance, silica, talc, stearic acid, magnesium or calcium stearate and/or
10 polyethylene glycols; or they may also contain binders, such as, for example, starches, gelatine, methylcellulose, gum arabic, tragacanth, polyvinylpyrrolidone; disintegrating agents, such as, for instance, starches, alginic acid, alginates; effervescing mixtures;
15 dyestuffs; sweeteners; wetting agents, such as, for instance, lecithin, polystorbates, laurylsulfates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured
20 in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.
Also the other pharmaceutical formulations containing the compounds of the invention may be prepared by known

methods and they can be, for example, syrups or drops for the oral administration, sterile solutions for injection, or suppositories.

In the following Examples, Example 2, Examples 3 to 11 together and Examples 12 to 13 together illustrate the preparation of a 2R,3R or 2S,3S enantiomer of a compound of formula (I) or of a pharmaceutically acceptable salt thereof. Example 14 illustrates a pharmaceutical composition incorporating such an enantiomer.

10 Where unspecified the $[\alpha]_D$ values are for 1% concentrations in 95% ethanol.

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Example 1

To a solution of 2- \bar{A} -(2-ethoxy-ph noxy)-benzyl $\bar{7}$ -morpholine
(\pm) RS,RS diastereoisomer (1.6 g) in anhydrous thanol,
methanesulphonic acid (0.33 ml) was added. By dilution with
5 diethyl ether (200 ml) a solid precipitated. This was
collected by filtration to give 2- \bar{A} -(2-ethoxy-phenoxy)-
-benzyl $\bar{7}$ -morpholine methanesulphonate m.p. 146-147°C,
U.V. (MeOH): $\lambda_{\text{max}} = 275 \text{ nm}$; $E_{1\text{cm}}^{1\%} = 50$, as the (\pm) RS,RS ra-
cemic form.

10 Example 2

An aqueous solution of (\pm) RS,RS 2- \bar{A} -(2-ethoxy-phenoxy)-
-benzyl $\bar{7}$ -morpholine methanesulphonate (m.p. 146-147°C; 40 g),
made basic with potassium carbonate, was extracted twice
15 with ethyl acetate. The organic solution was washed with
water, dried on sodium sulphate and evaporated to dryness
under vacuo. The free base (31 g) was dissolved in anhydrous
ethanol (140 ml) and to the solution L(+) mandelic acid
(15.06 g) dissolved in anhydrous ethanol (140 ml) was added.
The precipitate was filtered to give 18.85 g of a solid
20 having m.p. 134-151°C and $[\alpha]_D^{20} = (-) 48.01$ (1% solution in
80% ethanol). After crystallization from anhydrous ethanol
(200 ml), 16.86 g of a product (mandelate salt), melting at
151-153°C, were obtained; $[\alpha]_D^{20} = + 49.09$ (1% solution in
80% ethanol). This mandelate salt was dissolved in H₂O, the
25 solution was basified with potassium carbonate and the base
extracted with ethyl acetate. The organic solution was
dried over sodium sulphate and evaporated to dryness under
vacuo. The oily residue consisting of (-) 2S,3S-2- \bar{A} -(2-

-ethoxy-phenoxy)-benzyl-morpholin (12.15 g) was taken up with ethanol and an ethanolic solution of methanesulphonic acid (3.72 g) was added. After dilution with diethyl ether a precipitate formed which was filtered to give (+) 2S,3S-
 5 -2- $\bar{\alpha}$ -(2-ethoxy-phenoxy)-benzyl-morpholine methane sulphonate (13.05 g); m.p. 100-102°C, $[\alpha]_D^{20} = +21.89^\circ$ (1% solution in 95% ethanol).

Molar purity (D.S.C.) = 98%.

N.M.R. (CDCl₃) δ : 1.42 (t, 3H, CH₃-CH₂),
 10 2.71 (s, 3H, CH₃SO₃⁻),
 2.84-3.50 (m, 4H, CH₂-N-CH₂),
 3.85-4.40 (m, 3H, CH₂-O-CH),
 4.05 (q, 2H, CH₂-O-Ar),
 5.14 (d, 1H, O-CH-Ar),
 15 6.64-6.92 (m, 4H, Ar-C),
 7.33 (m, 5H, Ar-CH),
 9.20 (bs, 2H, NH₂).

The same method was used to prepare, starting from D(-) mandelic acid, the levo isomers (-) 2R,3R-2- $\bar{\alpha}$ -(2-ethoxy-
 20 -phenoxy)-benzyl-morpholine and (-) 2R,3R-2- $\bar{\alpha}$ -(2-ethoxy-phenoxy)-benzyl-morpholine methanesulphonate, the latter having m.p. 100-102°C, $[\alpha]_D^{20} = -21.69^\circ$ (1% solution in 95% ethanol).

By proceeding analogously, the following enantiomers were
 25 prepared starting from the corresponding (±) RS,RS racemic forms:

- (+) 2- $\overline{\alpha}$ -(2-methoxy-phenoxy)-benzyl $\overline{7}$ -morpholine;
(-) 2- $\overline{\alpha}$ -(2-methoxy-phenoxy)-benzyl $\overline{7}$ -morpholine;
(+) 2- $\overline{\alpha}$ -(4-trifluoromethyl-phenoxy)-benzyl $\overline{7}$ -morpholine;
(-) 2- $\overline{\alpha}$ -(4-trifluoromethyl-phenoxy)-benzyl $\overline{7}$ -morpholine;
5 (+) 2- $\overline{\alpha}$ -(2-methoxy-phenoxy)-benzyl $\overline{7}$ -morpholine methane-
sulphonate;
(-) 2- $\overline{\alpha}$ -(2-methoxy-phenoxy)-benzyl $\overline{7}$ -morpholine methane-
sulphonate;
(+) 2- $\overline{\alpha}$ -(4-trifluoromethyl-phenoxy)-benzyl $\overline{7}$ -morpholine
10 methanesulphonate;
(-) 2- $\overline{\alpha}$ -(4-trifluoromethyl-phenoxy)-benzyl $\overline{7}$ -morpholine
methanesulphonate.

The optical purity of the (+) 2S,3S- and (-) 2R,3R-2- $\overline{\alpha}$ -
-(2-ethoxy-phenoxy)-benzyl $\overline{7}$ -morpholine methanesulphonates
15 obtained from the (\pm) RS,RS racemic form was determined as
reported below.

To a solution of (+) 2S,3S-2- $\overline{\alpha}$ -(2-ethoxy-phenoxy)-benzyl $\overline{7}$ -
-morpholine base (1 g) (obtained from the corresponding
(\pm) RS,RS diastereoisomer) and Et_3N (0.90 ml) in anhydrous
20 toluene (40 ml), L(-) menthoxy-acetyl-chloride (0.60 ml)
in anhydrous toluene (10 ml) was added dropwise under
vigorous stirring at 10°C temperature. After stirring
1 hour at room temperature, the reaction was complete and
the reaction mixture was washed with water, dried over
25 sodium sulphate and evaporated to dryness under vacuo.

The same procedure was applied to the (-)-2R,3R-enantiomer obtained from (±) RS,RS 2- α -(2-ethoxy-phenyl)-benzyl-morpholine.

Each of the two diastereoisomeric amides so obtained was analysed by HPLC technique /Partisil PXS 10/25; cyclohexane:ethylacetate 93:7 with 0.15% of isopropylamine/ to give a Retention Time (R.T.) of 15.13 min. and, respectively, of 17.23 min.

The result was in both cases a relative purity $\geq 98.5\%$ from which an optical purity $\geq 97\%$ for both the (+) and (-) enantiomers may be inferred.

Example 3

A solution of 3.8 g (13.3 mmole) of (+) 2S,3R-phenyl-glycidic acid D(+)- α -methyl-phenethylamine salt was treated with 6.65 ml (13.3 mmole) of 2N HCl. The organic acid was extracted with diethylether and the solvent removed in vacuo after drying over Na_2SO_4 . The residue was dissolved in 70 ml of CH_2Cl_2 and 2 ml (14.3 mmole) of triethylamine were added. The solution was cooled to 0°C and 1.36 ml (14.3 mmole) of ethyl-chlorocarbonate were added dropwise under stirring during 1 hr. After 2 hr the solution was slowly added under stirring to a suspension of 2.26 g (59.7 mmole) of sodium borohydride in 17 ml of absolute ethanol, at 0°C. After 0.5 hr the temperature was allowed to rise to room temperature and stirring was continued overnight.

The mixture was poured into water and the product extracted with CH_2Cl_2 . After separation on a flash chromatography column (CHCl_3 : CH_3OH 100:2 as eluant) 0.62 g (31%) of (+) 2R,3R-cinnamyl alcohol-2,3-epoxide were obtained as a colorless oil; $[\alpha]_D^{20} = +45.9^\circ$ (C 1.5, abs. ethanol).
5 (Found: C, 71.68; H, 6.71. $\text{C}_9\text{H}_{10}\text{O}_2$ requires C, 71.97; H, 6.71%);

$^1\text{H-N.M.R.}$ (CDCl_3) δ : 3.24 (1H, dd, $-\text{CH}-\text{CH}_2\text{OH}$),
3.76 (1H, dd, $\text{CH}_A\text{H}_B-\text{OH}$),
10 3.94 (1H, d, $\text{Ph}-\text{CH}$, $J=2.1$ Hz),
4.05 (1H, dd, $\text{CH}_A\text{H}_B-\text{OH}$),
7.35 (5H, s, Ph);

IR (CHCl_3) cm^{-1} : 3590-3450 (OH), 1600, 1490 (arom. C=C),
1220, 1060 (Alk-O-Alk, Alk-OH);
15 0.33 g (15.3%) of the starting (-)-(2S,3R) phenyl glycidic acid were recovered together with 0.92 g (36.5%) of its ethyl ester.

Example 4

To a solution of 1.77 g (44.3 mmole) of NaOH in 100 ml of water, 16.4 g (133 mmole) of 2-ethoxy-phenol were added.
20 The mixture was stirred at 70° under nitrogen until the solid completely dissolved, and then 6.7 g (44.3 mmole) of (+) 2R,3R-cinnamyl alcohol-2,3-epoxide were added in 10 min. The solution was stirred at 70°C for 2.5 hr and then
25 poured into 200 ml of 1N NaOH at $10-15^\circ$. After extraction with CH_2Cl_2 the organic solution was washed successively

with 1N NaOH and brine. Elimination of the solvent gave
10.2 g of (+) 2R,3S-3-(2-thoxy-phenoxy) 1,2-dihydroxy-3-
-phenylpropane, $[\alpha]_D^{20} = +7.8^\circ$; m.p. 87-89°;
IR (KBr) cm^{-1} : 3440-3380 (OH), 1590, 1490 (arom.C=C),
5 1240 (Ar-O-Alk).

Example 5

To a solution of 10 g (34.6 mmole) of (+) 2R,3S-3-(2-
-ethoxy-phenoxy)-1,2-dihydroxy-3-phenylpropane in 100 ml
of pyridine, 6.44 g (34.0 mmole) of 4-nitro-benzoyl-
10 chloride in 100 ml of pyridine were added at -10° in
1.5 hr. After 0.5 hr the solution was poured into a
mixture of 2 l of 2N HCl and 1300 g of ice and the oily
precipitate was extracted with ethyl acetate. After an
usual work-up the compound (+) 2R,3S-3-(2-ethoxy-phenoxy)-
15 -2-hydroxy-1-(4-nitro-benzoyloxy)-3-phenylpropane (6.2 g)
was obtained as oil. $[\alpha]_D^{20} = +11.7^\circ$.

Example 6

To a solution of 60 g (16.2 mmole) of (-) 2R,3S-3-(2-
-ethoxy-phenoxy)-2-hydroxy-1-(4-nitro-benzoyloxy)-3-
20 -phenylpropane and 3.86 ml (27.4 mmole) of triethylamine
in 90 ml of CH_2Cl_2 , 1.54 ml (20.0 mmole) of $\text{CH}_3\text{SO}_2\text{Cl}$ were
added dropwise at 0-5° and the solution was kept for 0.5 hr
at that temperature. After washing with 10% HCl and 5%
NaHCO₃ solutions and water, the solution was dried over
25 Na₂SO₄ and the solvent evaporated to dryness.

After usual work-up the compound (+) 2R,3S-3-(2-ethoxy-phenoxy)-2-mesyloxy-1-(4-nitrobenzoyloxy)-3-phenylpropane (7.5 g) was obtained as oil, $[\alpha]_D^{20} = +33.6^\circ$.

Example 7

- 5 A solution of 3.95 g (7.7 mmole) of (+) 2R,3S-3-(2-ethoxy-phenoxy)-2-mesyloxy-1-(4-nitrobenzoyloxy)-3-phenylpropane in 40 ml of dioxane and 16 ml of 2N NaOH was stirred for 4 hr at room temperature. After diluting with 200 ml of water the solution was extracted with ethyl acetate and the
10 organic phase washed with a 5% aqueous solution of NaHCO_3 then water. After evaporation of the solvent in vacuo the residual oily epoxide (-) 2S,3S-3-(2-ethoxy-phenoxy)-3-phenylpropane 1,2-epoxide weighed g. 2.05 (100%) and was used as such for the subsequent step, $[\alpha]_D^{20} = -3.1^\circ$.

15 Example 8

- A solution of 2.05 g (7.6 mmole) of (-) 2S,3S-3-(2-ethoxy-phenoxy)-3-phenylpropane 1,2-epoxide in 50 ml of methanol and 30 ml of 32% NH_4OH was kept standing in a sealed flask for 6 hr. After evaporation of the solvent the residue was
20 dissolved in ethyl acetate, and 0.52 ml (8 mmole) of $\text{CH}_3\text{SO}_3\text{H}$ in 10 ml of ethyl acetate were added to the solution. After 16 hr 2.13 g of a crystalline product (+) 2S,3S-1-amino-3-(2-ethoxy-phenoxy)-2-hydroxy-3-phenylpropane was collected, m.p. 97-99°C, $[\alpha]_D^{20} = +34.4$.

Example 9

To a solution of 2.13 g (7.4 mmole) of the aminoalcohol
(+) 2S,3S-1-amino-3-(2-ethoxy-phenoxy)-2-hydroxy-3-phenyl-
propane and 2.27 ml (16.2 mmole) of triethylamine in
5 70 ml of CH_2Cl_2 kept at -5 to -10° , 0.64 ml (8.0 mmol) of
chloroacetylchloride dissolved in 20 ml of CH_2Cl_2 were
added dropwise. After 0.5 hr the solution was washed with
water, dried over Na_2SO_4 and evaporated to dryness.
After usual work-up a residue of (-) 2S,3S-1-chloroacetyl-
10 amino-3-(2-ethoxy-phenoxy)-2-hydroxy-3-phenylpropane (2.6 g)
was obtained as oil, $[\alpha]_D^{20} = +16.6^\circ$.

Example 10

To a solution of 2.0 g (18.0 mmole) of potassium t-butoxide
in 15 ml of tert-butanol, 3.3 g (9.0 mmole) of (-) 2S,3S-1-
15 -chloroacetyl-amino-3-(2-ethoxy-phenoxy)-2-hydroxy-3-phenyl-
propane in 40 ml of tert-butanol were added at room tempe-
rature in 2 hr. After a further hour, 8% HCl was added until
pH 4-5 was reached and the solution was evaporated to
dryness in vacuo. The residue was taken up with water, the
20 solution was neutralized with solid NaHCO_3 and extracted 5
with ethyl acetate. The organic phase was thoroughly washed
with water, dried over Na_2SO_4 and the solvent distilled
in vacuo. An oily residue was obtained of (-) 2S,3S-6- α -(2-
-ethoxy-phenoxy)-benzyl]-morpholin-3-one (2.6 g),
25 $[\alpha]_D^{20} = -21.2^\circ$.

Example 11

To a solution of 5.0 g (15.3 mmole) of (-) 2S,3S-6- α -(2-ethoxy-phenoxy)-benzyl-7-morpholin-3-one in 200 ml of anhydrous toluene, 12.7 ml (45.4 mmole) of 70% toluene solution of RED-AL (Vitrade), diluted with 40 ml of anhydrous toluene were added at room temperature in 15 min. After 4 hr the excess RED-AL was decomposed with 20 ml of 2N NaOH. The organic phase was separated, washed with water, dried, and evaporated to dryness. The residue was dissolved in ethyl acetate and 1.0 ml (15.4 mmole) of $\text{CH}_3\text{SO}_3\text{H}$ was added to the solution. After standing overnight at room temperature, the solid (+) 2S,3S-2- α -(2-ethoxy-phenoxy)-benzyl-7-morpholine methanesulphonate was collected by filtration; 4.9 g obtained, m.p. 100-102°C; IR (KBr) cm^{-1} : 3000-2400 (NH_2), 1590-1495 (arom.C=C), 1250 (Ar-O-Alk), 1205 (Alk-O-Alk), 1190, 1040 (SO_3H); $[\alpha]_D^{20} = +21.81^\circ$.

Example 12

The (+) 2S,3S-2- α -(2-ethoxy-phenoxy)-benzyl-7-morpholine (3.2 g) was dissolved in anhydrous ethanol (50 ml), then a slight excess of an ethanolic solution of hydrochloric acid was added. The solvent was evaporated to dryness under vacuo and diethyl ether was added to the oily residue. The solid obtained after grinding was filtered to give (+) 2S,3S-2- α -(2-ethoxy-phenoxy)-benzyl-7-morpholine hydrochloride (3.3 g) m.p. 138-140°C. By proceeding analogously, the following (+) and (-)

enantiomer hydrochlorides were obtained:

(-) 2R,3R-2-[α -(2-thoxy-phenoxy)-benzyl]-morpholine hydrochloride, m.p. 138-140°C;

5 (-) 2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine hydrochloride;
 (-) 2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine hydrochloride;

(-) 2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine hydrochloride; and

10 (-) 2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine hydrochloride.

Example 13

Tablets were prepared, each weighing 200 mg and each containing 5 mg of active ingredient, in the manner described below:

15

Composition (for 10,000 tablets)

(-) 2S,3S-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate, the dextro (-) enantiomer deriving from the (±) RS,RS racemic form

20

Lactose	50 g
Corn starch	1,250 g
Talc (powdered)	450 g
Magnesium stearate	50 g
	20 g.

25

The (-) 2S,3S-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine methanesulphonate, the lactose and half of the corn starch

were mixed, sieved through a 0.55 mm mesh screen.

30 g of corn starch was dispersed in 300 ml of hot water.

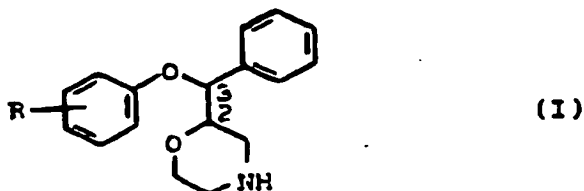
The mixture of the powders was granulated with the starch mucilage obtained. The granulate was dried and passed

5. through a 1.4 mm mesh screen. The rest of the starch was added, as also the talc and the magnesium stearate.

A careful blending was performed and the mass was compressed into tablets with 8 mm diameter punches.

CLAIMS

1. A 2R,3R or 2S,3S enantiomer of a compound of formula (I):



wherein

5 R is a C₁-C₆ alkoxy group or a trihalomethyl group; and the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein R is methoxy, ethoxy, or trifluoromethyl.

3. A compound according to claim 1 or 2, wherein the
10 enantiomer is a dextro (+) enantiomer.

4. A compound according to claim 1 or 2, wherein the enantiomer is a levo (-) enantiomer.

5. A compound according to claim 3 selected from the group consisting of:

15 (+)2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine;
(+)2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine;
(+)2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine,
and pharmaceutically acceptable salts thereof.

6. A compound according to claim 4 selected from the group consisting of:

(-)-2-[α -(2-methoxy-phenoxy)-benzyl]-morpholine;

(-)-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine;

5 (-)-2-[α -(4-trifluoromethyl-phenoxy)-benzyl]-morpholine,
and pharmaceutically acceptable salts thereof.

7. A compound according to any one of the preceding claims which is a hydrochloride salt.

8. A compound according to any one of claims 1 to 6
10 which is a methanesulphonate salt.

9. A compound according to claim 5 which is
(+)-2-[α -(2-ethoxy-phenoxy)-benzyl]-morpholine or a
pharmaceutically acceptable salt thereof.

10. A compound according to claim 9 which is the
15 hydrochloride salt.

11. A compound according to claim 9 which is the
methanesulphonate salt.

12. A process for the preparation of a compound
according to any one of the preceding claims, which process
20 comprises:

(a) reacting the (\pm)-RS,RS racemic form of a compound of

formula (I), as free base, with an optically active acid so obtaining a mixtur of two diaster isomeric salts;

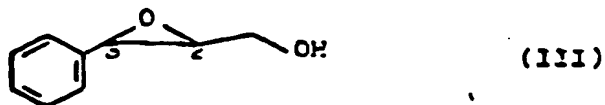
- (b) separating the obtain d salts by crystallization;
- 5 (c) optionally liberating the dextro (+) or levo (-) enantiomeric base from the respective separated salt; and
- (d) optionally salifying the obtained dextro (+) or levo (-) enantiomeric base with a pharmaceutically
- 10 acceptable acid.

13. A process for the preparation of a compound according to any one of claims 1 to 11, which process comprises:

- (a) reducing the (+) or (-) enantiomer of a glycidic
- 15 acid of formula (II):



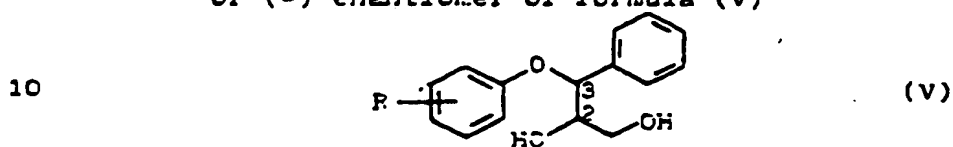
or a derivative thereof, so obtaining the (+) or (-) enantiomer of the cinnamyl alcohol-2,3-epoxide of formula (III)



- 5 (b) reacting a (+) or (-) enantiomer of formula (III) with a phenol derivative of formula (IV)

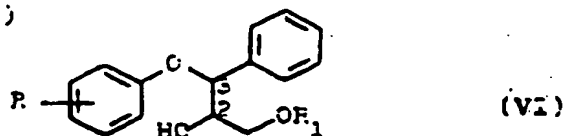


wherein R is as defined in claim 1, so obtaining a (-) or (+) enantiomer of formula (V)



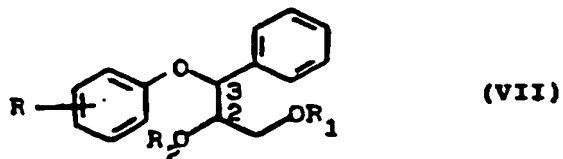
wherein R is as defined above;

- 10 (c) esterifying a (+) or (-) enantiomer of formula (V) with a carboxylic acid, or a reactive derivative thereof, so obtaining a (+) or (-) enantiomer of formula (VI)
- 15



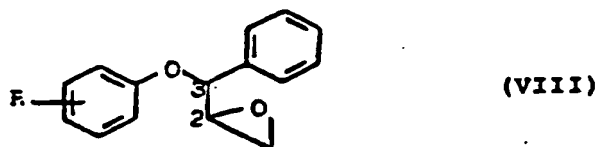
wherein R is as defined above and R₁ is the residue of a carboxylic acid;

- 20 (d) esterifying a (+) or (-) enantiomer of formula (VI) with a sulphonic acid, or a reactive derivative thereof, so obtaining a (+) or (-) enantiomer of formula (VII)



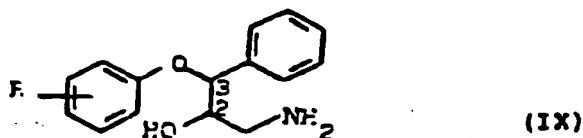
wherein R and R₁ are as defined above and R₂ is the residue of a sulphonic acid;

- (e) making an epoxide from a (+) or (-) enantiomer of formula (VII) in the presence of a base so obtaining a (+) or (-) enantiomer of formula (VIII)



wherein R is as defined above;

- (f) reacting a (+) or (-) enantiomer of formula (VIII) with ammonia, so obtaining a (+) or (-) enantiomer of formula (IX)

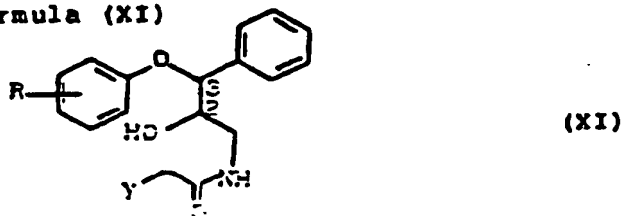


wherein R is as defined above;

- (g) reacting a (+) or (-) enantiomer of formula (IX) with a compound of formula (X)

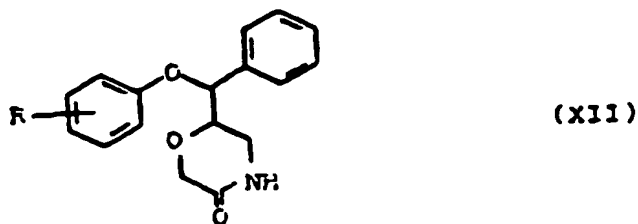


wherein Y is halogen, so obtaining a (+) or (-) enantiomer of formula (XI)



where x in R and y as defined above;

- (h) cyclizing (+) or (-) enantiomer of formula (XI) so obtaining a (+) or (-) enantiomer of formula (XII):



5 wherein R is as defined above; and

- (i) reducing a (+) or (-) enantiomer of formula (XII) so obtaining a (+) or (-) enantiomer of formula (I) and, if desired, converting the obtained 2R,3R or 2S,3S enantiomer of formula (I) into a pharmaceutically acceptable salt thereof.

10 14. A pharmaceutical composition comprising a
compound according to any one of the claims 1 to 11 as
active ingredient and a pharmaceutically acceptable
carrier and/or diluent.

15. A compound according to claim 1 for use in a
15 method of treatment of the human or animal body by
therapy.

16. A compound according to claim 15 for use as an anti-depressant.

17. A compound according to claim 15 for use in treating sleep disorders or as a minor tranquilizer.

18. A process for the preparation of a compound as claimed in claim 1, said process being substantially as
5 hereinbefore described in Example 2, Examples 3 to 11 together or Examples 3 to 12 together.

19. A pharmaceutical composition substantially as hereinbefore described in Example 13.

20. A 2R,3R or 2S,3S enantiomer of a compound of
10 formula (I) as defined in claim 1 and bioprecursors thereof.

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